Epitomes

Important Advances in Clinical Medicine

Internal Medicine

The Scientific Board of the California Medical Association presents the following inventory of items of progress in internal medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in internal medicine that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Internal Medicine of the California Medical Association and the summaries were prepared under its direction.

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Intraarterial Chemotherapy

COLORECTAL CANCER affects 138,000 new patients and is responsible for approximately 60,000 deaths each year in the United States alone. Most patients who die of colorectal carcinoma have liver metastases, and for many the liver is the only clinical site of metastatic tumor. Chemotherapy for patients with metastatic disease consists of the fluorinated pyrimidines 5-fluorouracil (5-FU) and fluorodeoxyuridine (FUDR, or floxuridine). While 5-FU and floxuridine produce objective response rates of about 20% when given intravenously, neither has been proved to provide a survival advantage over no treatment.

A number of factors predict that 5-FU or floxuridine given via the hepatic artery may be superior to intravenous delivery in patients with liver-only metastasis from colorectal carcinoma. The blood supply of hepatic metastasis is primarily via the hepatic artery, whereas a normal liver receives a dual blood supply from the hepatic artery and portal vein. Thus, administering 5-FU or floxuridine into the hepatic artery exposes hepatic metastasis to a higher concentration of drug than normal liver tissue. Pharmacologic properties of 5-FU and floxuridine that may make hepatic artery therapy more effective include a favorable dose-response curve and high rates of first-pass hepatic extraction (80% and 95%, respectively), thus minimizing systemic toxicity. The cell-cycle phase-specific activity of 5-FU and floxuridine predicts increased cytotoxicity with long-term drug use such as is achievable with continuous infusion. The recent development of a reliable, implantable, continuous infusion pump has made hepatic artery infusion chemotherapy practicable. For these reasons, hepatic artery infusions, usually with floxuridine, have become an active area of clinical investigation.

The reported series of colorectal cancer patients treated with hepatic artery infusion have either been uncontrolled or historically controlled and are difficult to assess because they use a broad range of methods and criteria to measure response. Computed tomography, especially when done with volumetrics, is the single most objective and reliable index of disease response or progression. Radionuclide liver scans are reproducible but difficult to quantify in determining response. Although physical examination, liver enzymes and carcinoembryonic antigen levels are all unreliable methods of measuring the response of colorectal cancer metastatic to the liver, they have been used in many studies as indicators of disease response. Despite these frequently inexact methods of assessing response, the available studies of hepatic artery infusion of floxuridine have found impressive response rates ranging from 29% to 88%. In addition, some of these studies report superior durations of survival when compared with historical control groups. Whether these improved rates of response and survival are the result of variations in the tumor burden at the initiation of therapy, the methods of assessing response, the use of inappropriate control groups or of the efficacy of treatment is uncertain.

Hepatic artery infusion of floxuridine is associated with significant toxic effects, especially biliary sclerosis, which occurs in most patients. Recent evidence suggests that the "chemical hepatitis" reported previously may in fact have been biliary sclerosis. This is a serious toxic effect and has been documented by cholangiography, liver biopsy and at postmortem examination. It is heralded by elevation of the alkaline phosphatase level, and a doubling of the alkaline phosphatase level requires at least delaying further administration of the drug until the levels return to normal, with attenuation of further doses. The anatomic changes of biliary sclerosis are presumably not reversible and may contribute to drug-related mortality, although the associated elevations in alkaline phosphatase and bilirubin levels may resolve with the early withdrawal of therapy.

Gastric and duodenal inflammation and ulceration and cholecystitis are other complications of hepatic artery infusion of floxuridine. These complications appear to be related to the incidental perfusion of the involved organs by floxuridine. The frequency of the gastric and duodenal complications can be minimized at the time of pump implantation by ligating the gastroduodenal artery and collaterals that arise distal to the point of cannulation of the hepatic artery. Most investigators recommend routine cholecystectomy at the time of placement of the infusion pump to prevent the development of drug-induced cholecystitis.

No prospectively randomized studies comparing the efficacy and toxicity of intravenous with intraarterial administration of 5-FU or floxuridine have yet been completed. Appropriately designed, prospectively stratified, randomized trials comparing intravenous administration with hepatic artery infusion of chemotherapy for colorectal carcinoma metastatic to the liver only are in progress in the Northern California Oncology Group (headquarters in Palo Alto) and at the Memorial Sloan-Kettering Cancer Center (New York). Definitive conclusions regarding the precise role of hepatic arterial infusion chemotherapy must await the completion of these studies.

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The Routine Preoperative Chest X-ray Study

ACCORDING TO THE REPORT of a World Health Organization (WHO) Scientific Group, "There are some excellent studies on the futility of preoperative chest radiography," a conclusion that was reached after a comprehensive study of the relevant international medical literature. This opinion is endorsed by the Food and Drug Administration, the US Bureau of Radiological Health and most of the American specialist colleges and societies. If the results of a clinical examination are normal, no preoperative chest x-ray film is needed at any age for any surgical procedure. Moreover, even when there are clinical chest symptoms, there is little advantage to be gained in most cases because clinical judgment will decide the choice of anesthesia with as much accuracy as a chest x-ray study. Nor will postoperative management be affected by information gained from a preoperative chest film, which is not only not cost-effective but increases the radiation given both to an individual patient and to the population. Indeed, it is time that the routine chest film cease to be part of a routine physical examination, preoperatively or otherwise; the only exception may be in populations wherein chest disease is known to be prevalent.

The WHO Scientific Group on the Indications for and Limitations of Major X-Ray Diagnostic Investigations concluded that

> provided a careful clinical examination is made and there is no clinical evidence of chest disease, there is no indication for preoperative chest radiology. If the clinical examination discloses an abnormality, this in itself is not necessarily an indication for radiography. Such cases must be judged on their merits.

The available references are numerous; only a selection can be provided here.

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Fine-Needle Aspiration Biopsy of Thyroid

THYROID NODULES are common and about 4% or 40,000 per million persons in the United States have nodular goiters. Thyroid cancer, however, is rare: about 40 cases per million persons. Thus, great selectivity is necessary in deciding which nodules are likely to be malignant and to require aggressive surgical management.

Fine-needle aspiration biopsy of the thyroid has largely solved this dilemma. Introduced by Soderstrom in 1952, it has been used widely in Sweden, Europe and Japan. Only in the past ten years, however, with the development of a cadre of trained cytologists, has fine-needle aspiration biopsy been widely used in the United States.

Fine-needle aspiration biopsy of the thyroid is a simple office procedure, nontraumatic, acceptable to patients and easily repeated if necessary. If the aspirate is diluted with blood, or not enough thyroid tissue is obtained, it must be repeated. Other than an occasional tiny hematoma at the site of aspiration, there have been no complications. There has been no spread of cancer with this technique.

A physician will usually receive one of three reports from the cytologist: (1) clearly malignant, (2) clearly benign or (3) follicular neoplasm or suspicious for neoplasm.

Papillary, medullary, anaplastic and metastatic neoplasms are easily diagnosed and, if present, require surgical confirmation and appropriate therapy. Clearly benign lesions include involutionary nodules, benign thyroid nodules, chronic lymphocytic thyroiditis (Hashimoto's thyroiditis), subacute thyroiditis and multinodular goiter. Patients with these lesions are usually treated with levothyroxine to suppress thyroid-stimulating hormone and growth. Follicular neoplasms are usually benign (about 85%) but occasionally malignant (15%). If the lesion is large (more than 2 cm), firm or has shown recent growth, it should be surgically removed. If it is small and soft, the patient can be given a trial of thyroxine therapy for three to six months. If the lesion fails to regress or grows, then it should be removed. Cysts of the thyroid can